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THE SYNTHESIS OF 4β-HYDROXYCHAMAECYNONE AND 4α-HYDROXYISOCHAMAECYNONE

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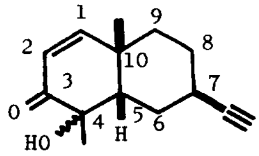
The acetylenic nor-sesquiterpene alcohol named "hydroxyisochamaecynone" has been isolated from the essential oil of Benihi tree (Chamaecyparis formosensis Matsum., Cupressaceae) as a minor constituent, together with the related acetylenic compounds (1, 2). On the base of the spectral evidence, the structure of this alcohol has been inferred as shown in (I) having the cis-decaline skeleton with the steroid conformation, except the configuration of the hydroxyl group at C-4.

We now wish to report the synthesis of 4β-hydroxychamaecynone (Ia) and its C-4 epimer, 4α-hydroxyisochamaecynone (Ib) with the object of establishing the structure of "hydroxyisochamaecynone".

The acetylenic ketone (II) prepared from α-santonin by means of the previously reported method (3) was used as the starting material. Treatment of II with isopropenyl acetate in the presence of p-toluenesulfonic acid produced an oily enol acetate (III) in 80% yield. Epoxidation of III with monoperphthalic acid at room temperature gave an epoxide (IV) (mp. 68~9°C after careful purification by chromatography).

Hydrolysis of the epoxide (IV) with 10% aqueous KOH solution in ethanol at room temperature gave a hydroxyketone (Va), mp. 95°C, in 42% yield from III; ir (CCl_4) (4), ν 3590 cm^{-1}, 3490, 3315, 2115, 1715; nmr (CCl_4), δ_{ppm} 1.27 (s), 1.45 (s), 1.90 (-CH-C≡C$\underline{H}$, d, J=2.5 Hz); ORD (MeOH), negative Cotton effect ($[\Phi]_{310}$, -1492; $[\Phi]_{260}$, + 2000; A=-35). On the other hand, thermal rearrangement of the epoxide (IV) at 180°C for 15 minutes under nitrogen atmosphere gave a keto-acetate (VI), whose hydrolysis with 10% aqueous KOH solution in ethanol at room temperature afforded an isomeric hydroxyketone (Vb), mp. 102.5°C, in 22.6% yield from III; ir (CCl_4), ν 3600 cm^{-1}, 3490, 3310, 2110, 1718; nmr (CCl_4), δ_{ppm}


1
2
3
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O
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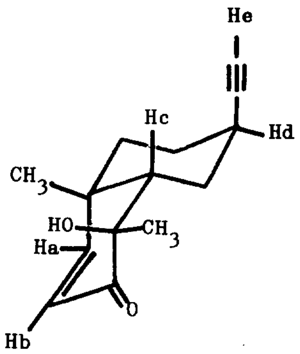
I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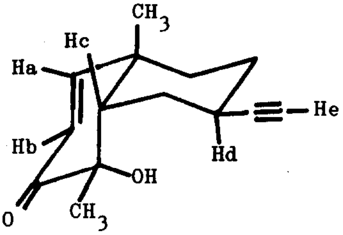
CH3
HO
CH3
Ha
Hb
O

Ia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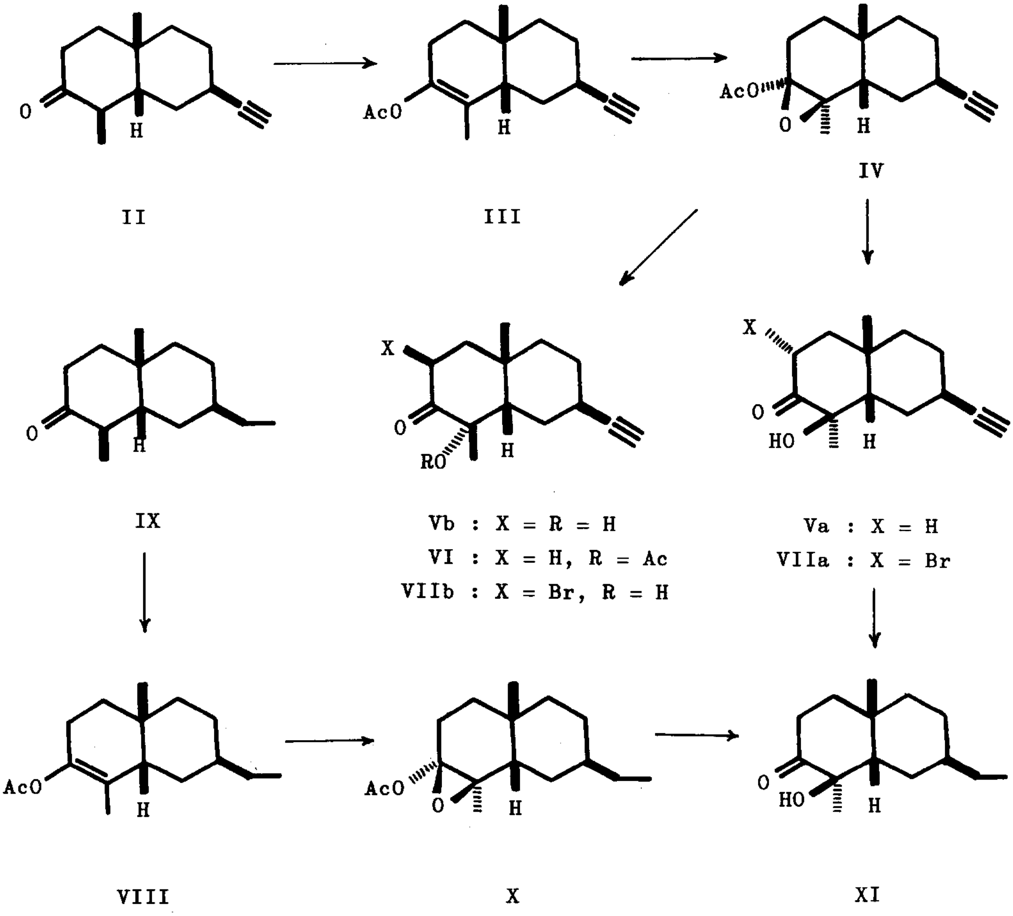
Hc
Ha
He
Hb
Hd
OH
O
CH3

Ib


O
H
II
AcO
H
III
AcO
O
H
IV
O
H
IX
X
O
RO
H
Vb : X = R = H
VI : X = H, R = Ac
VIIb : X = Br, R = H
X
O
HO
H
Va : X = H
VIIa : X = Br
AcO
H
VIII
AcO
O
H
X
O
HO
H
XI

1.22 (s), 1.25 (s), 1.92 ($-CH-C\equiv C\underset{\sim}{H}$, d, J=2.5 Hz). A consideration of the mechanism on thermal rearrangement of the epoxide (IV) (5) suggests that the hydroxyketone (Vb) must be the C-4 epimer of Va. Bromination of Va and Vb with bromine in acetic acid in the presence of hydrobromic acid at room temperature gave a sirupy monobromo compound (VIIa), in 36% yield, and a crystalline monobromo compound (VIIb), mp. 140.5°C, in 32.6% yield, respectively. The carbonyl absorptions in the infrared spectra ($CHCl_3$), and the nmr signals ($-CH_2-\overset{Br}{C\underset{\sim}{H}}-CO$); 1727 and 1730 cm^{-1} and 5.05 (1H, q, J=13, 7 Hz) and 5.53 ppm (1H, q, J=13, 7 Hz) for VIIa and VIIb, respectively, indicate that both compounds are α-bromoketones with the equatorial bromine atoms.

Dehydrobromination of VIIa with lithium bromide and lithium carbonate in dimethylformamide at 140°C gave Ia, mp. 71°C, in 45% yield; ir (CCl_4), ν 3580 cm^{-1} 3500, 3310, 2110, 1708 sh, 1684; uv, λ_{max}^{MeOH} 228 nm (ε=7400); nmr (100 MHz, CCl_4), δ_{ppm} 1.34 (s), 1.44 (s), 2.10 (Hc, m), 1.93 (He, d, J=3 Hz), 2.83 (Hd, m), 5.88 (Hb, d, J=10 Hz), 6.43 (Ha, q, J=10, 2 Hz). On the other hand, dehydrobromination of VIIb gave Ib, in 68% yield, identical with the natural product (I) in the mixed melting point, the thin-layer and gas chromatographic behavior, the infrared, nmr and mass spectra and the ORD curve; ir (CCl_4), ν 3590 cm^{-1}, 3500, 3310, 2110, 1710 sh, 1685; nmr (100 MHz, $CDCl_3$), δ_{ppm} 1.27 (s), 1.34 (s), 2.12 (He, d, J=2.5 Hz), 2.63 (Hd, m), 5.95 (Hb, d, J=9 Hz), 6.53 (Ha, d, J=9 Hz).

The non-steroid conformation with the axial acetylene group at C_7 for Ia is revealed from the nmr spectrum, which shows the long-range coupling, Jac=2 cps, between Ha and Hc (1,2) and a rather small magnitude of half-band width, 14 Hz, of Hd (2). The hydroxyl group at C_4 in Ia is assumed to be in β(axial)-configuration from its infrared spectrum showing the intramolecular hydrogen bonded and the associated hydroxyl absorptions at 3580 and 3500 cm^{-1}, respectively (6). In contrast to this, the steroid conformation with the equatorial acetylene group at C_7 and the α(axial)-hydroxyl group at C_4 is assigned for Ib from its nmr spectrum, in which no long-range coupling between Ha and Hc and a large magnitude of half-band width, 24 Hz, of Hd are observed, and from its infrared spectrum, which shows the intramolecular hydrogen bonded and the associated hydroxyl absorptions at 3590 and 3500 cm^{-1}, respectively.

The above conclusion was also confirmed by the chemical evidence. The configuration of the epoxy group in IV should determine the stereochemistry at C-4 in Ia and Ib. An examination with a Dreiding model give no information for the direction of the attack of peracid on III since it is not clear whether III exists in the steroid conformation or in the non-steroid one; in the former the β-side is apparently less sterically hindered, whereas in the latter a difference in steric hindrance between the β- and the α-side is very small. However, in the enol acetate (VIII) with the more bulky ethyl group at C_7, the steroid conformation with the β(equatorial)-ethyl group is more stable form than the non-steroid one with the β(axial)-ethyl group (1), therefore, epoxidation is expected to occur on the β-side. Epoxidation of VIII, prepared from hexahydroisochamaecynone (IX) (1), with monoperphthalic acid gave an epoxide (X), which was hydrolysed with alkali to give a hydroxyketone (XI), mp. 91.5°C; ir (CCl_4), ν 3595 cm^{-1}, 3475, 1713, in 17.3% yield from IX. The tetrahydro derivative obtained by catalytic hydrogenation of Va was identical with (XI) in the mixed melting point and the infrared and nmr spectra. This indicate that the hydroxyl group of Ia is in β-configuration.

From the above mentioned evidence, the structure of the natural compound "hydroxyisochamaecynone" was determined to be 4α-hydroxyisochamaecynone (Ib).

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